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How a Vaccine Search Ended in Triumph

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Nuns and Jews, cow warts and rabbit horns.

The common link: they were all crucial elements in the search for the world's newest vaccine.

There are fascinating stories behind every advance in medicine, be it hand washing or brain surgery. But the 70-year history behind the creation of a vaccine against human papillomavirus, which causes cervical cancer, is more fraught than most with blind alleys, delicate moments, humor and triumph.

Although cervical cancer is being beaten in rich countries thanks to Pap smears, it is still a great killer of the world's poor. Fulminating tumors that can hemorrhage the womb or burst the intestine make death every bit as agonizing as it was for our great-grandmothers. Even in wealthy countries, aggressive forms appear in rare cases, forcing women barely in their 20's to get hysterectomies.

For all of those women, the new vaccine approved in June by the Food and Drug Administration could be a lifesaver. But creating it was no easy task. It took decades for scientists to even figure out the cause: the papillomavirus, named for the papilla, or bud, that the tumor creates.

Species as different as birds and whales have their own papillomas. There are more than 100 human strains. Many are harmless. Some cause warts on hands, noses or genitals, and some cause cancer. As a result, blame has been laid on origins like toads, witchcraft and God's anger at promiscuous women.

Against that background of superstition, the two newest vaccines use technologies that sound almost like science fiction.

Gardasil, made by Merck, uses a yeast to grow the proteins that form the outer shell of the virus; every batch of 360 proteins almost magically assembles itself into a soccer ball exactly mimicking the shell's shape.

Its rival, Cervarix by GlaxoSmithKline, produces the same protein, with the same power, in an insect virus grown in a broth of caterpillar ovary cells.

But each step forward to those techniques was a triumph of hard science over the pseudoscientific myths that for centuries surrounded the disease.

The first was posited by a doctor in Florence in 1842. He noticed that prostitutes and married women died of cervical cancer, but nuns almost never did. Though he might have discerned that it was sexually transmitted, he was thrown off by another fact: nuns often died of breast cancer. His conclusion was that nuns' corsets were dangerously tight.

One may laugh, but prominent American scientists made a similar error in the 1970's, noting that many women with cervical cancer had a history of genital herpes. Instead of realizing that it was a coincidence, they erroneously concluded that the herpes virus was the cause. And they were closer to the mark than 1950's researchers, who had blamed smegma, which builds up under the foreskin of men who do not wash.

Research that could have led them in the right direction was done in the 1930's by Dr. Richard Shope of the Rockefeller University, who on a hunting trip heard a friend describe seeing rabbits with "horns," which were actually large warts.

Dr. Shope asked his friend to send some of the horns. He then ground them up, filtered them through porcelain that let only tiny virus-size particles through, and injected the filtrate into other rabbits, which grew horns in turn.

"Incidentally, that's where the jackalope myth comes from," said Dr. William Bonnez, who was part of the University of Rochester's vaccine development team. (Jackalopes, jackrabbits with antelope horns, are made by taxidermists and appear on things like postcards from Wyoming. But references to horned rabbits go back centuries, and their condition probably stemmed from papilloma infections.)

Dr. Shope's work showed the cause was a virus, but it was not until the 1980's that DNA amplification allowed a German researcher, Dr. Harald zur Hausen, to pin down papilloma as the cause.

"That was really the pivotal point," said Dr. Douglas R. Lowy, chief of the cellular oncology laboratory at the National Cancer Institute and part of a team whose subsequent work led to the vaccine. "Before that, the field suffered from the boy-who-cried-wolf phenomenon, as in people would say, 'Last year you said it was herpes virus, now you say it's papilloma; why should we believe you?' "

In the interim between Drs. Shope and zur Hausen, another line of inquiry was going on. Researchers were stumped as to why cervical cancer was so rare among Jewish women.

It had been noted as far back as 1901 that at Leeds General Infirmary and London Hospital, cancer of the cervix "was seldom or never met with among the numerous Jewesses," according to a Lancet article of the time.

More pseudoscientific myths arose trying to explain that. (The Lancet writer, whose thesis was that salt caused cancer, believed that Jews were protected by avoiding bacon.) But it took the founding of Israel, drawing Jewish women from all over the world, to debunk them.

The long-held assumption that circumcision was protective was disproved by high cancer rates among Muslim women, who had circumcised husbands, and by relatively low rates among Soviet Jewish women, who often did not. Another myth, that abstaining from sex during menstruation helped prevent the disease, was dispelled by comparing Orthodox women who abstained to others who did not. As with non-Jews, the apparent risk factors for the few Israeli women with the disease were multiple sexual partners and poverty.

Work by Dr. Joseph Menczer of the Wolfson Medical Center in Israel showed that genes were the crucial factor. A protective configuration of the p53 gene is much more common among Jews, except for those from North Africa, the one subgroup likely to contract cervical cancer.

In the 1980's, with many teams in hot pursuit of a vaccine, a stumbling block emerged. Human warts contain very little virus.

In Rochester, Dr. Bonnez's solution was to approach veterinarians treating dairy cows, which grow grapefruit-size warts loaded with virus. He still has a block of 20-year-old cow warts in his freezer.

First, he had to make a blood test for the virus. A control group of people who had never had sex was needed. Once again, nuns were at the fore of cervical cancer research. The Sisters of St. Joseph in Rochester were "really very supportive," Dr. Bonnez said, answering questionnaires about their sexual histories and giving blood samples.

"People were snickering, ha-ha, nuns, no sex," he said. "But having a base control group of 50 subjects — that led me to realize the bovine approach was wrong."

Instead, said Robert Rose, an immunologist working with Dr. Bonnez, the Rochester team tried grafting bits of foreskin collected from hospital circumcisions and infected with genital wart extract into mice lacking the ability to reject foreign tissue. The resulting cysts contained enough human virus to work with.

Ultimately, the two vaccines were the fruit of the labors of dozens of scientists. A patent battle involving the National Cancer Institute, the University of Rochester, Georgetown University and Queensland University in Australia was resolved after 13 years when Merck and Glaxo signed royalty agreements with all four.

Dr. Lowy, of the National Cancer Institute, said one of his most rewarding moments during the years of research also involved rabbits. He was in Paris, at the Pasteur Institute, where a model vaccine was being tested. All the rabbits that had been given the vaccine were disease free, he said, while 95 percent of those that had been given a placebo had cancerous lesions.

"The fact that it worked so well," he said, "was just incredible."